REMARKS

Applicants have received and reviewed the Office Action dated August 20, 2008. By way of response, Applicants have withdrawn claim 2 without prejudice. No new matter has been added. Claims 1, 3-12, 21-23 are pending. Claims 1, 3-5, 10-12 have been amended. Support for the amended claims can be found at least at Table 2, Table 3, within the sequence listing, and in SEQ ID NO.: 1-43 in paragraphs 0041 to 0044 of the specification. New claims 21-23 have been added. Support for the added claims can be found at least at Table 2, Table 3, within the sequence listing, and in SEQ ID NO.: 1-43 in paragraphs 0041 to 0044 of the specification.

Claims 1, 3-5, 7 and 10-12 were objected to due to informalities. These claims have been amended to overcome the Examiner's objections.

Specification

The Examiner notes that the title "Novel Use" at the top of the first page of the specification is inconsistent with the title in the Application Data Sheet. We thank the Examiner for bringing this to our attention. The title has been amended to correspond with the title in the Application Data Sheet.

The Examiner notes that the specification does not contain as a first paragraph a claim to benefit of priority to any application. According to 37 CFR 1.76(b)(5), providing the claim to benefit of priority in the application data sheet (ADS) constitutes the specific reference required and need not otherwise be made part of the specification. Applicants have referenced U.S. provisional application 60/538,512, filed January 26, 2004 in the ADS. Nevertheless, the Applicants thank the Examiner and have provided a paragraph claiming priority in the Amendments to Specification section of this response.

In review of the application, Applicant's noticed that paragraph 0057 of the description inadvertently contained Applicant notes. We have presented an amended paragraph 0057 in the

Amendments to Specification section of this response. This amendment does not add any new subject matter to the application.

35 U.S.C. § 112

Claims 1-3 and 5-11 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. A simple administration of an effective amount of the selected agonist is a straightforward experiment and can easily be accomplished with little experimentation. Applicants submit that the use of the claimed sequences are not known for this indication, the simple administration method as presently claimed is well known in the art and is straight forward to a skilled artisan. In fact, Examiner admits the specification enables peptides of the presently claimed invention. A specification that enables may still require experimentation to make and use an invention. The specification is enabling and does not require undue experimentation to select the amount for a selected agonist and practice the presently claimed invention. We respectfully traverse.

To meet the enablement requirement of 35 U.S.C. §112, first paragraph, a specification must contain a sufficient description to enable one skilled in the art to make and use the claimed invention. *See, e.g., Chiron Corp. v. Genentech, Inc.,* 363 F.3d 1247, 1253 (Fed. Cir. 2004); MPEP §2164.01. A specification does not need to explicitly disclose every detail, and may omit what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP §2164.01. To make and use an invention may require experimentation even if the specification is enabling. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984); MPEP §2164.01. The experimentation must not be unduly extensive, however, costly and timely experimentation alone does not constitute undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988).

The Examiner admits that the specification is enabling for a method of ameliorating symptoms associates with the growth of bone-metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising an effective

amount of PTH receptor against, which is human parathyroid hormone 1-84, human parathyroid 1-34, or an analogue thereof, to reduce bone loss, bone fracturing, and/or reduce pain.

While a number of agonists are disclosed, selecting one and using it is not difficult experimentally. The presently claimed invention comprises both PTH 1-84 and PTH 1-34. PTH molecules are well known in the prior art. Amino acids 1-6 comprise the activation domain and amino acids 25-34 comprise the binding domain. Paragraph [0010]. Further, PTH molecules of less than 25 amino acids are essentially inactive. Paragraph [0010]. The receptor binding domain, the activation domain, and the necessary number of amino acids for activation are all well known. The present application discloses an animal model for metastatic bone disease in which molecules of the presently claimed invention can be measured. Paragraphs [0073-0084]. Further, the application incorporates WO O3/105772. Paragraphs [0048-0051]. WO 03/105772 teaches methods for determining the IC_{50}, methods for determining the stimulation of adenylate cyclase activity, and methods of determining *in vivo* bone anabolic activity. Paragraphs [0097-0107]. Further, WO 03/105772 discloses IC_{50} and adenylate cyclase activity for molecules of the presently claimed invention.

The prior art and the present application disclose activation domains, binding domains, necessary amino acids for activation, in vivo and in vitro methods of testing the claimed invention, and the data from these tests for molecules of the claimed invention. Based on the prior art and the present application a skilled artisan could select an agonist and an effective amount and successfully practice the method of the presently claimed invention without undue experimentation.

The Examiner admits Barbier et al. teaches the use of PTH analogues for treating osteoporosis. The Examiner points to Rabbini et al. and Yin et al. for the premise that peptide analogues vary dramatically in bioactivity and that PTHrP is increased in patients with solid tumors and hypercalcemia.

As presented above, the prior art and the present application disclose activation domains, binding domains, necessary amino acids for activation, in vivo and in vitro methods of testing the claimed invention, and the data from these tests for molecules of the claimed invention. Based on the prior art and the present application a skilled artisan could successfully practice the method of the presently claimed invention without undue experimentation.

In view of the above amendments and remarks, Applicants believe the present claims are enabled and in condition for allowance.

35 U.S.C. § 102(b)

Claims 1-4, 6, 7 and 10-12 were rejected under 35 U.S.C. § 102(b) as anticipated by Hock, WO 01/21198. The presently claimed invention is a method for ameliorating pain associated with the growth of bone metastasized cancer or bone-originated cancer. Hock discloses a method of reducing the risk of cancer in a patient who is susceptible to acquiring cancer. In summary, treating pain is not the same as preventing carcinogenesis. The method of treating a patient for pain and a method of reducing cancer are not the same invention. Applicants submit that Hock does not teach the pain reduction of the presently claimed invention. We respectfully traverse for at least the above reasons.

In order to anticipate a claim, the prior art reference must teach each and every element of the claim. *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987; MPEP § 2131).

It is the Examiner's position that Hock teaches a method of reducing the risk of cancer in a subject by administering a parathyroid hormone, such as rhPTH (1-34). In deed, Hock states "The method of the invention benefits a subject at risk of developing cancer by decreasing the probability that the subject gets cancer" (pp 7, lines 28-29). Hock further states "If left untreated, a cancer typically invades other tissues, spreads, and eventually results in death. By reducing the incidence of cancer, the present invention prevents or reduces the likelihood of this invasion, spread, and death" (pp 8, lines 3-5). Hock teaches the use of parathyroid hormone for

reducing the risk of developing cancer in patients who do not have cancer but are at risk of developing cancer. In Hock's only example (pp. 20-21) patients were identified for selection in the study based on their likelihood of developing cancer, not on whether they were already suffering from cancer. In deed, the inclusion criteria included postmenopausal women with a minimum of one moderate or two mild atraumatic vertebral factures. The criteria for evaluation centered on bone measurements like bone mineral density, height, bone biopsy, spine x-ray, etc. In fact, there were no criteria for evaluation based on a decrease in the size or number of tumors. The only measurement related to cancer was if a tumor developed or not. It is our position that Hock discloses a method of reducing the risk of cancer in a patient who is susceptible to acquiring cancer.

By contrast, an embodiment of the presently claimed invention is a method of ameliorating pain associated with the growth of bone metastasized cancer or bone-originated cancer. Thus, the presently claimed invention is limited to patients who are suffering from bone metastasized cancer or bone-originated cancer.

It is the Examiner's position that a method of Hock can ameliorate the damage from metastasis to bone, particularly when the spread to bone has caused a significant defect in the bone (pp. 8, lines 15-17). However, the Hock specification does not provide any support for the administration of PTH receptor agonist to a patient suffering from bone metastasized cancer or bone-originated cancer to reduce pain. All of Hock's subjects are free of cancer.

In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation. *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008) (citing *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1379 (Fed. Cir. 2007)). In other words, the prior art must enable the claimed invention. *Minn. Mining & Mfg. Co. v. Chemque, Inc. (3M)*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

The Hock specification discloses the administration of PTH to a patient who is susceptible to acquiring cancer. The only example, including disclosed and claimed dosage

requirements, are directed to the administration of PTH to patients without cancer. The Hock specification does not enable a skilled artisan to practice the administration of PTH on patients suffering from bone metastasized cancer or bone-originated cancer to reduce pain.

It is the Examiner's position that Hock inherently discloses the amount of PTH effective to reduce pain. We disagree. A method of treating a patient for pain and a method of reducing cancer are not the same invention. Certainly the subjects of the treatment are different. Hock's subjects are cancer free. Thus, reducing pain in patients suffering from bone metastasized cancer or bone-originated cancer cannot be inherent in Hock's method of reducing cancer in patients who are susceptible to acquiring cancer. They are two different and distinct inventions.

The principle of "inherency," in the law of anticipation, requires that any information missing from the reference would nonetheless be known to be present in the subject matter of the reference, when viewed by persons experienced in the field of the invention. *Hitzeman v. Rutter*, 243 F.3d 1345, 1355 (Fed. Cir. 2001) ("consistent with the law of anticipation, an inherent property must necessarily be present in the invention described by the count, and it must be so recognized by persons of ordinary skill in the art"); *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (that a feature in the prior art reference "could" operate as claimed does not establish inherency). Thus, when a claim limitation is not explicitly set forth in a reference, evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268 (Fed. Cir. 1991). Inherency requires certainty and cannot tolerate and degree of chance. Since Hock's subjects are cancer free, the inherent treatment of a cancer victim is very unlikely.

A method of treating a patient for pain and a method of reducing cancer are not the same invention. Thus, reducing pain in patients suffering from bone metastasized cancer or bone-originated cancer cannot be inherent in Hock's method of reducing cancer in patients who are susceptible to acquiring cancer. Further, even if the inventions were similar, Hock must still establish that reduction of pain is both necessarily present and recognized by a person of ordinary skill in the art when PTH is being administered to a patient suffering from bone

metastasized or bone-originated cancer. Hock acknowledges the use of PTH to reduce fracture and increase stiffness and toughness. Hock discloses the use of PTH to reduce cancer through administration to a patient who is highly susceptible to acquiring cancer. Nowhere does the Hock specification enable the use of PTH for administration to a patient suffering from bone metastasized or bone-originated cancer. Nowhere does the Hock specification contemplate or recognize the use of PTH to reduce pain. Nowhere does the Hock specification provide dosage or administration schedules directed to the reduction in pain. In fact, Hock states "Therefore, any daily dose of hPTH (1-34) in the range of greater than 6ug to at least about 40ug would be effective for reduction of the risk of cancer." pp 18, lines 3-6. Further, Hock states "daily doses above about 40ug are less preferred than does of 40ug or less." pp 18, lines 8-9. Thus, Hock has determined an acceptable dosage range for hPTH (1-34) for reducing the risk of cancer. Hock has not determined the acceptable dosage range of the presently claimed molecules when used to reduce pain in a patient with symptoms associated with bone metastasized cancer or bone-originated cancer. The reduction in pain limitation of the presently claimed invention is not inherent within the Hock specification because it is not necessarily present nor would it be recognized by a person of ordinary skill in the art.

For at least the above reasons, Applicants believe the present claims are in condition for allowance.

35 U.S.C. § 103(a)

Claims 8 and 9 were rejected under 35 U.S.C. § 103(a) over Hock in view of McKenna et al. (J. Bone Joint Surg. Am., 1966, 48:1-26). Claims 8 and 9 are dependent on an allowable claim and are in turn allowable. The presently claimed invention is a method for ameliorating pain associated with the growth of bone metastasized cancer or bone-originated cancer. Hock discloses a method of reducing the risk of cancer in a patient who is susceptible to acquiring cancer. McKenna merely discloses that pain is a symptom associated with sarcomas but suggests no treatment.

PTH (1-34) is sold under the brand name FORTEO®. A copy of the prescribing information is attached. The drug FORTEO (PTH 1-34) contains a warning label that, in summary, states the drug FORTEO® should not be used in a subject that has been diagnosed with bone cancer or other cancers that have spread (metastasized) to the bones. See the prescribing information, page 1. Therefore, to the skilled man, a method of treating a patient for pain associated with bone metastasized cancer or bone-originated cancer with PTH receptor agonists is exactly opposite of what the prior art, taken as a whole, suggests. Further, a method of treating a patient for pain and a method of reducing cancer are not the same invention. We respectfully traverse for at least the above reasons.

"Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). *See also KSR*, 127 S. Ct. at 1734 ("While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls.") The U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). The Court did not, however, discard the TSM test completely; it noted that its precedents show that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.*

Hock discloses the administration of PTH to a patient who is susceptible to acquiring cancer. McKenna discloses that patients suffering from osteogenic sarcoma have symptoms that include pathological bone pain. The Examiner argues that the combination of these two

references meets all the elements of the presently claimed invention. We disagree and reference our arguments presented above. Hock does not disclose a method of ameliorating symptoms associated with the growth of bone metastasized cancer or bone-originated cancer to reduce pain. Mckenna only states that pathological pain is one symptom of osteogenic sarcoma and does not discuss the use of PTH receptor agonists effective to reduce pain.

It is the Examiner's position that it would have been obvious to combine these two references. We disagree. A method of treating a patient for pain and a method of reducing cancer are not the same invention. Further, under the brand name FORTEO®, PTH (1-34) is indicated for the treatment of osteoporosis. Studies in rats demonstrated that PTH (1-34) (teriparatide acetate) demonstrated an increased risk of osteosarcoma or malignant bone tumor that was dependant on dose and treatment duration. Accordingly, FORTEO® is known to be contraindicated for individuals who are at increased risk for osteosarcoma or who have bone cancer or other cancers that have metastasized to bone. In fact, the FORTEO website (www.forteo.com/public/login/login.jsp) warns:

> As part of drug testing, teriparatide, the active ingredient in FORTEO, was given to rats for a significant part of their lifetime. **In these studies, teriparatide caused some rats to develop osteosarcoma, a bone cancer.** Osteosarcoma in humans is a serious but very rare cancer. Osteosarcoma occurs in about 4 out of every million older adults each year.

Further the FORTEO® warning states: Do Not Use FORTEO® if you have ever been diagnosed with bone cancer or other cancers that have spread (metastasized) to the bones, have received radiation therapy involving the bones, or have certain bone diseases. Patients who have a bone disease should tell their doctor.

Even if a combination of Hock and McKenna did meet all the elements of the presently claimed invention, and we maintain they do not, a skilled artisan would not be motivated to combine the two references for at least the reasons given on the FORTEO® label. There is no reason why the skilled artisan would be motivated to combine the two references or have any expectation of success if combined. The FORTEO® label clearly states that PTH should not be

used to treat patients that have been diagnosed with bone cancer or other cancers that have spread to the bones or that have certain bone diseases. To the contrary, the presently claimed invention is a method of ameliorating symptoms associated with the growth of bone metastasized cancer or bone-originated cancer through administration of a PTH receptor agonist effective to reduce bone pain.

For at least the above reasons, Applicants believe the present claims are in condition for allowance.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

22 Dec 2008
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